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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,879	06/27/2003	Lieven Stuyver	BJS-2551-123	5237

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EXAMINER	
PENG, BO	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
11/23/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,879	STUYVER ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18,20,22,24,26,28,29,35,36 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16,18,20,22,24,26,28,29,35* is/are allowed.

6)☒ Claim(s) *,36 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 8, 2010 and November 10, 2010, has been entered.

2. Based on the supplemental amendment, filed on November 10, 2010, Claims 1-15, 17, 19, 21, 23, 25, 27, 30-34, 37, 38 and 40 have been cancelled. Claims 16, 18, 20, 22, 24, 26, 28, 29, 35, 36 and 39 are pending. Claims 18, 20, 22, 24, 26 and 28 were withdrawn as nonelected.

Allowable Subject Matter and Rejoinder

3. Claims 16, 28, 29 and 35, directed to a method of detecting HBV genotype A using a probe consisting of SEQ ID NO: 77, 140 or 193, are allowable. The probes are free of the prior art, and also in view of superior results of detecting genotype A HBV shown in the specification.

4. Since subcombination of Claims 16, 28, 29 and 35 are directed to an allowable method, the previously withdrawn combinations of methods of Claims 18, 20, 22, 24 and 26 (Groups II-VI) as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104. Because Claims 18, 20, 22, 24 and 26 of Groups II-VI, previously withdrawn from consideration under 37 CFR 1.142, have been rejoined, the restriction requirement as set forth in the Office action mailed on June 16, 2006, is hereby

withdrawn. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler,* 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

5. Accordingly, Claims 16, 18, 20, 22, 24, 26, 28, 29, 35, 36 and 39 have been considered in this Office action.

Claim Objection

6. **(Prior objection-moot)** The objection to Claim 38 under 37 CFR 1.75, as being a substantial duplicate of claim 29, **is moot** in view of the cancellation of the claim.

7. **(Prior objection-withdrawn)** The objection of Claims 35 and 36 **is withdrawn** in view of the amendment to the claims.

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **(Prior rejection-maintained)** The rejection of Claims 36 and 39 under 35 U.S.C. 112, first paragraph, as failed to provide an adequate description which probes and primers of 5 to 50 nucleotides in length can specifically identify HBV genotype-A-specific sequences, **is maintained** for the reason of record.

In response to Applicant's argument:

10. The applicants submit that the claims are supported by an adequate written description. Withdrawal of "written description" rejection of claims 36 and 29 is requested.

11. Applicant's asertion is not persiasive because Applicant has failed to provide any specific support for this assertion. As indicated in the previuos office action, the scope of new Claim 36 encompasses use of any undefined nucleotide probes of about 5 to 50 nucleotides long to specifically detect "the presence or absence of HBV genotype A", but not other HBV genotypes, in a sample. However, the cited primers of SEQ ID NO: 75, 76, 94, 104, 105, 112 and 134-135 are not genotype-specific. While the specification shows a few species of probes that can detect genotype A, the specification shows other nucleotide probes of about 5 to 50 nucleotides long probes detect other genotypes, rather than genotype A. This teaching by the specification indicate that not all nucleotide probes of about 5 to 50 nucleotides long can specifically detect "the presence or absence of HBV genotype A". The specification has failed to provide adquate description for the claimed subgenus of "nucleotide probes of about 5 to 50 nucleotides long probes" for specifically detecting "the presence or absence of HBV genotype A". The rejection is therefore maintained.

12. **(Prior rejection-withdrawn)** The rejection of Claims 16, 28, 29 and 35, 36 and 39 under 35 U.S.C. 112, first paragraph, as failing to comply with the scope of enablement

requirement **is withdrawn** in view of the amendment. Rejection of Claims 37, 38 and 40 is moot in view of the cancellation of the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. **(Prior rejection-restated)** Claims 36 and 39 are rejected under 35 U.S.C. 103(a) as being obvious over Maertens (WO 94/12670), and McDonough (EP056923A2, 1993, provided in the previous Office action), Okamoto (J. Gen Virol. 69, 2575-2583, 1988) and Norder (J. Gen Virology 73, 1201-12-8, 1992).

15. Maertens teaches a line probe assay (LiPA) for genotyping viruses, such as HCV, HIV, HBV and/**or** HTLV present in biological samples (see p. 25). Maertens teaches the method comprises the steps of providing at lease one of the probes of HCV and at least of one of the probes capable of detecting HIV, and/**or** HBV, and/**or** HTLV, possibly providing a set of primers to respectively amplify HIV, and/**or** HBV and/**or** HTLV by means of PCR, contacting the biological sample with the probes under conditions which allow hybridization between the probes and target sequences. Maertens specifically indicates that LiPA can be used for determining the type of HBV characterized by incorporating on one and the same strip, probes hybridizing specific to HBV mutants or HBV core, pre-core (see p. 26). Maertens teaches that

the probes are immobilized in a line-wise fashion to a membrane strip for reverse hybridization.

16. Maertens does not explicitly teach detecting HBV genotype A specific sequence using a one nucleotide probe and the primers in Claim36.

17. Norder teaches the correlation of HBsAg sequence polymorphisms to HBV genotype A to F based on the comparison of the complete genomic sequences of 27 HBV strains (whole document, particularly Figure 5, p. 499). The genotype A HBV adw2, pBV933, shown in Fig. 5 has nucleic acid sequence 100% identical to the instant SEQ ID NO: 280 (see attached sequence alignment). Norder specifically points out the different amino acids in each genotype, see e.g. Figure 5 and Para bridge 496 and 497; and also in *Discussion*).

18. Okamoto teaches 18 HBV strains, which are classified as genotype A to D, wherein genotype A HBV clone 2, pHBV933, has a nucleic acid sequence 100% identical to the instant genotype A HBV SEQ ID NO: 280, as evidenced by the attached sequence alignment.

19. McDonough teaches a method of detecting of HBV subtype A, such as HBV*adw*, using amplification oligonucleotides and hybridization probes. McDonough's method comprises the step of amplifying HBV with oligonucleotide primers, and the step of hybridizing HBV nucleic acids obtained directly or amplified HBV nucleic acids. McDonough indicates that the HBV probes hybridize the genotype A HBV, HBV*adw*, as cited in Ref. Ono *et al* 1983, Nuc. Acids Res. 11(6):1747-1757 (see 2, l.35-l.40). Also as evidenced, Okamoto indicates that that pHBV933 of HBVadw disclosed by Ono is genotype A, see Description of Figure 1, p. 2578. pHBV933 of HBVadw disclosed by Ono has a nucleic acid sequence 100% identical to the instant genotype A HBV SEQ ID NO: 280, see the attached sequence alignment.

20. McDonough teaches use of primers for detecting HBV, wherein SEQ ID NO: 5 is

complementary to the instant SEQ ID NO: 75, see alignment below:

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McDonough SEQ ID NO:5     GTTCCATACAACGGGCAAACAGGAG
       SEQ ID NO:75       CAAGGTATGTTGCCCGTTTGTCC
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21. It would have been obvious to one of ordinary skill in the art to modify Maertens' method to detect the presence of HBV genotype A in a biological sample using a genotype-specific probe designed based on known HBV genotype A sequence taught by Norder and Okamoto. One would have been motivated to do so given the knowledge that line probe assay can be used to genotype HBV, as taught by Maertens. There would have been a reasonable expectation of success given the knowledge of HBV genomes of different genotypes as taught by Norder and Okamoto. Maertens's method of detecting specific viral nucleic acids using hybridization probes has general applicability. Because a nucleotide is a nucleotide, no matter what virus produced it, it will hybridize to complementary sequence of a probe. Since both Norder and Okamoto provide nucleic acid sequences of HBV genotypes, it is within the ability of one of ordinary skill in the art to select specific probes from known HBV sequences of different genotypes to determine genotype A-specific sequences. Primer/probe design is a routine practice for one of skill in biological laboratories, as illustrated by Maertens.

22. It would also have been obvious to one of ordinary skill in the art to amplify the HBsAg region using a suitable primer pair in order to detecting HBV in a sample as taught by Maertens and McDonough. One would have been motivated to do so and have a reasonable expectation of success because McDonouh has shown how to detect HBV by amplifying HBV using suitable primers. Given that HBV sequences are taught by Norder and Okamoto, it is within the ability of one of skill in biology art to make primer/probe based a known HBV sequence as illustrated by McDonough. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary

skill in the art at the time the invention was made.

In response to Applicant's argument:

23. The applicants submit that the four primers as indicated amplify the HBsAg region of many different genotypes in a very efficient way, as described in the remarks of record, where after the A type may be genotyped as indicated and all other genotypes may be genotyped as well. The use of these primers is an unexpected advantage of the claimed invention. The applicants note that LiPA HBV genotyping kits are commercially available from the Assignee and based on the presently claimed invention and offer a reliable DNA test which offers the means to genotype HBV A-H.

16. This argument is considered but found not persuasive. First, the claims recite 8 primers. In the argument, Applicant fails to indicate which four primers "amplify the HBsAg region of many different genotypes in a very efficient way". Secondly, Applicant has also failed to indicate to which specific commercially available LiPA HBV genotyping kits applicant refers. As a result, it is not clear how evidence support the alleged "unexpected" results of four primers. Third, in contrast to Applicant's assertion of "unexpecyed result", the cited primers SEQ ID NOs: 75, 76, 94, 105, 112, 134 and 135 appear to overlap with HBV genomes of other genotypes see Specification, Fig. 1., indicating that the cited primers are not genotype-specific. Applicant has not shown that these non-genotype-specific primers, recited in the claim 36, would result in the intended result of "determining the presence or absence of HBV genotype A in a biological sample". Thus, Applicant's argument without factual evidence is not persuasive.

Remarks

17. Claims 16, 18, 20, 22, 24, 26, 28, 29 and 35 are allowable.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on Tu-F, 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/BO PENG/
Primary Examiner, Art Unit 1648